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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/626,731	CO ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 3/8/04, has been entered.
Claims 1, 4, and 9 have been amended.
Claims 12-23 have been added.

Claims 1-23 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 3/8/04.
The rejections of record can be found in the previous Office Actions.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15-23 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:
"15(c) contacting the donor cells with an immunoglobulin specific to B7-1 and an immunoglobulin specific to B7-2, wherein the immunoglobulin specific to B7-2 has a higher affinity for B7-2 than hCTLA4Ig and the immunoglobulin specific to B7-1 has a higher affinity for B7-1 than hDTLA4Ig".

Applicant's amendment, filed 3/8/04, directs support to page 6, line 20 – page 7, line 10 and page 45, lines 20-25 for the above-mentioned "limitation".

However page 45, paragraph 2 of the instant specification discloses that anti-B7-2 alone inhibited T cell proliferation on all days tested at a level comparable to hCTLA4Ig and that it is the combined anti-B7-1 and anti-B7-2 antibodies that reflected a higher affinity compared to CTLA4Ig.

Therefore, the written description of the specification as filed does not provide for either an anti-B7-1 or anti-B7-2 antibody alone having a higher affinity compared to CTLA4Ig.

The specification as filed does not provide a sufficient written description of this "limitation". The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations", as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06

5. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the 3D1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

6. Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-23 are indefinite in the recitation of "3D1" because its characteristics are not known. The use of "3D1" antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "3D1" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct hybridomas or cell lines .

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-3, 6-17 and 20-23 are rejected under 35 U.S.C. § 102(b) as being anticipated by Blazar et al. (WO 95/34320) (1449) (see entire document) essentially for the reasons of record.

Applicant's amended claims and arguments, filed 3/8/04, have been fully considered but are not found convincing essentially for the reasons of record set forth in previous Office Actions.

Applicant asserts that the claims now recite "wherein the immunoglobulin specific to B7-2 can compete with the murine antibody 3D1 for binding to B7-2" which is not anticipated by the prior art anti-B7-2 antibodies.

Upon reconsideration of applicant's arguments that page 23, paragraph 1 of Blazar et al. describes "folloring this priming step, the inhibitory agent(s) are added to the culture, e.g., after about 18 to 36 hours of priming, the inhibitory agents can be added fro several hours to the culture prior to transplantation of cells into the recipient", the prior art rejection with respect to claims 4-5 and 18-19 have been withdrawn under 35 USC 102(b).

For examination purposes, the broadest reasonable interpretation of "competes with the murine antibody 3D1 for binding to B7-2" reads on the inhibitory anti-B7-2 antibodies of the prior art. Such costimulatory inhibitory agents would have had the inhibitory property of competing with the 3D1 antibody, given that the prior art and instant 3D1 anti-B7-2 antibodies appear to have the same or nearly the same costimulatory inhibitory properties. Applicant has not provided objective evidence to distinguish the costimulatory inhibitory properties between the instant 3D1 and prior art anti-B7-2 inhibitory antibodies. Comparison of the instant products with prior art is difficult since the Office is not equipped to manufacture the claimed product and/or prior art products that appear to be related and conduct comparisons. It is the burden on applicant to distinguish between the instant 3D1 and prior art anti-B7-2 inhibitory antibodies. Also, it is noted that the prior art antibodies do not have to bind the exact same epitope as the instant 3D1 antibody, provided that the prior art anti-B7-2 can compete with the instant 3D1 antibody.

The following of record is reiterated for applicant's convenience

Applicant essentially argued that Blazar et al. do not teach contacting the donor cells with B7-1-specific / B7-2-specific antibodies and recipient cells from the patient for a period of time of "from about 1 to about 48 hours before being introduced into the patient".

Applicant acknowledged that Blazar et al. Teach saturating B7 with inhibitors such as hCTLA-4Ig and anti-LFA-1 for 3 hours.

However, applicant asserted that the claims are not drawn to "inhibitors" but rather drawn to "contacting the donor cells with an immunoglobulin specific to B7-1 and an immunoglobulin specific for B7-2 ... from about to 1 to 48 hours".

It has been acknowledged that the Blazar's Examples of CTLA-4Ig is not an immunoglobulin and that anti-LFA-1 antibodies do not recognize B7-1 nor B7-2.

In addition, applicant asserted that Blazar teaches a priming step of contacting donor and recipient cells for 2.5-4 days before the mixture is contacted with CTLA-4Ig and anti-LFA-1, which is distinguishable from the claimed limitation of "contact for a period of time from about 1 to 48 hours".

Although applicant pointed to the teaching of incubating donor and recipient cells with antibodies for about 2.5 to 4 days by Blazar et al., Blazar et al. teach saturating B7 with inhibitors such as hCTLA-4-Ig and anti-LFA-1 for 3 hours (see pages 28-29, overlapping paragraph). Therefore, Blazar et al. does teach saturating B7 with inhibitors with the newly added claimed limitations (e.g. 3 hours).

It is noted that the claimed methods recite "comprising" which does not exclude additional, unrecited elements or method steps. See MPEP 2111.03.

Again, Blazar et al. teach the use of inhibitors including those that bind both B7-1 and B7-2 (e.g. Summary of the Invention, including page 4, paragraph 1; Detailed Description of the Invention, including page 6 - page 7, paragraph 1, page 17, paragraph 1 and Uses of the Invention, page 11, paragraph) to induce T cell unresponsiveness for bone marrow transplantation, including its use for the treatment of hematological malignancies and anemia (e.g. see Background of the Invention, Summary of the Invention and Uses of the Invention).

In addition, Blazar et al. teach the inhibitory agents can be administered for 18-36 hours after T cell priming e.g. see page 23, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. Bone marrow comprise lymphocytes, stem cells and immature blood cells. The claimed functional limitations and constructions encompassed by the claims would be inherent properties of the referenced methods to induce T cell responsiveness with B7-1 and B7-2-specific antibodies for bone marrow transplantation in the treatment of malignancies and anemia.

Further, it is noted that Blazar teaches recombinant, including humanized antibodies (see Antibodies on pages 9-15, particularly pages 13-15).

Applicant's arguments have not been found persuasive.

11. Claims 1-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320) (1449) alone or in combination with Chappel et al. (U.S. Patent No. 6,096,537), Dinsmore et al. (U.S. Patent No. 5,919,449) and Goldberg et al. (Transplant Immunology 2: 27-34, 1994) essentially for the reasons of record.

Applicant's amended claims and arguments, filed 3/8/04, have been fully considered but are not found convincing essentially for the reasons of record set forth in previous Office Actions.

Applicant's arguments and the examiner's rebuttal concerning applicant's assertions that the claims now recite "wherein the immunoglobulin specific to B7-2 can compete with the murine antibody 3D1 for binding to B7-2" which is not anticipated by the prior art anti-B7-2 antibodies have been addressed above.

The following of record is reiterated for applicant's convenience.

Dinsmore et al. was been added herein to support the position that the prior art provides sufficient motivation and expectation of success for providing an inhibitory antibody to meet the individual need and professional of the judgment of the person administering or supervising the administration of the compositions to achieve the desired immunosuppressive effects, including prior treatment for one to three days (e.g. see entire document, including columns 15-17) and exemplifies modifying cells to be transplanted with an antibody for one hour (see Example III, on column 20).

Goldberg et al. teach the pretreatment of renal transplants with inhibitory antibodies to prolong allograft survival and teach the ex vivo pretreatment of said inhibitory antibodies can occur from 20 minutes to 14 hours and employed 1 hour for subsequent studies (See entire document, including page 31, Determination of optimal concentration of perfused antibody).

Therefore, Dinsmore et al. and Goldberg et al. provide further evidence that the ordinary artisan modified transplants ex vivo with inhibitory antibodies for various times, including those times encompassed by the claimed invention, to achieve the immunosuppression of deleterious immune responses to the grafted cells, tissues and organs.

Again, applicant argued that Blazar uses the 3 hour incubation period after a priming step of 2.5-4 days (see Blazar, page 28, line 33-page 29, line 12) and asserts that a priming step is not recited in the claims.

Again, applicant argued that Blazar teaches away from performing an in vitro incubation step targeting only one pathway.

It is noted that the claimed methods recite "comprising" which does not exclude additional, unrecited elements or method steps. See MPEP 2111.03

Again, applicant argued that Chappel does not teach nor suggest the ex vivo application of antibodies to B7-1 or B7-2 in a method of transplanting cells. Therefore, applicant asserts that Chappel merely suggest the use of a 30 minute in vitro incubation step with reagents that target molecules distinct from the claimed invention.

In teaching combined in vitro and in vivo treatment regimens, Blazar et al. teach the agents serve to inhibit T cell proliferation, T cell signaling T cell costimulation or T cell adhesion (e.g. see page 22, paragraph 2).

In teaching the use of suitable agents or antibodies, Chappel teach that the antibody pretreatment serves to inhibit or prevent rejection of the transplanted cells or tissues.

As indicated previously and above, Blazar et al. teach the use of inhibitors including those that bind both B7-1 and B7-2 (e.g. Summary of the Invention, including page 4, paragraph 1; Detailed Description of the Invention, including page 6 - page 7, paragraph 1, page 17, paragraph 1 and Uses of the Invention, page 11, paragraph) to induce T cell unresponsiveness for bone marrow transplantation, including its use for the treatment of hematological malignancies and anemia (e.g. see Background of the Invention, Summary of the Invention and Uses of the Invention). In addition, Blazar et al. teach the inhibitory agents can be administered for 18-36 hours after T cell priming e.g. see page 23, paragraph 1). Bone marrow comprise lymphocytes, stem cells and immature blood cells. The claimed functional limitations and constructions encompassed by the claims would be intrinsic properties of the referenced methods to induce T cell responsiveness with B7-1 and B7-2-specific antibodies for bone marrow transplantation in the treatment of malignancies and anemia.

Although applicant pointed to page 28, lines 20-32 for the teaching of incubating donor and recipient cells with antibodies for about 2.5 to 4 days by Blazar et al., Blazar et al. teach saturating B7 with inhibitors such as hCTLA-4-Ig and anti-LFA-1 for 3 hours (see pages 28-29, overlapping paragraph and Experiment 3 on page 31). Therefore, Blazar et al. does teach saturating B7 with inhibitors with the newly added claimed limitations (e.g. 3 hours).

Blazar et al. differs from the claimed methods by not disclosing the range of about 1- 24 hours per se. Given the teaching of Blazar et al., including saturating B7 with inhibitors such as hCTLA-4-Ig and anti-LFA-1 for 3 hours (see pages 28-29, overlapping paragraph and Experiment 3 on page 31). It is noted that Experiment 3 on page 31 discloses that the inclusion of the priming step in the treatment regiment can increase the inhibitory effects of the agents.

Given the teaching of Blazar et al. that the in vitro incubation step with agents that block B7 factors the development of donor anti-host specific hyporesponsiveness (In vitro incubation of splenocytes with agents on pages 28-29) with the example of 3 hours (pages 28-29 and 31), one of ordinary skill in the art would been motivated to select those times of incubating donor cells with B7-specific inhibitors to achieve donor anti-host specific hyporesponsiveness, consistent with the claimed therapeutic endpoints. One of ordinary skill in the art would have appreciated that various times in including times of about 1 -24 hours would have been suitable depending on the nature of the donor cells and the nature of the agents and conditions suitable to achieve donor anti-host specific hyporesponsiveness.

In addition, it is noted that Chappel et al. teach masking antigens to achieve or to induce immunological nonresponsiveness can be for 30 minutes (see entire document, including column 8, paragraph 1 and column 18, paragraph 1), which reads on "about 1 hour" of the claimed methods. It is noted that Chappel et al. exemplify masking murine pancreatic islet cells and not the mixture of cells taught by Blazar et al. or that encompassed by the claimed methods.

As pointed out above, Dinsmore et al. and Goldberg et al. provide further evidence (e.g. one hour, 20 minutes to 14 hours) that the ordinary artisan modified transplants ex vivo with inhibitory antibodies for various times, including those times encompassed by the claimed invention, to achieve the immunosuppression of deleterious immune responses to the grafted cells, tissues and organs

Given the prior art teachings of Blazar et al., Chappel et al., Dinsmore et al. And Goldberg et al., one of ordinary would have been motivated to pretreat donor cells for a period of time to achieve or to induce donor anti-host specific hyporesponsiveness. Given such teachings, one of ordinary skill in the art would have expected that a range of times, including that encompassed by the claimed "about 1-24 hours" would have been met at the time the invention was made given the nature of the donor cells, and to achieve the desired immunosuppressive goal to prolong transplant survival.

Given the teachings of the prior art references, including the Examples described by Blazar et al., Chappel et al, Dinsmore et al. and Goldberg et al.; one of ordinary skill in the art would have appreciated that achieving immunological nonresponsiveness by pretreating donor cells with B7-specific inhibitors would have varied depending on the nature of the donor cells, the nature of the agents and the conditions suitable for achieving said immunological nonresponsiveness.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention, including a range of "about 1 - 24 hours" or pretreating donor cells with B7-specific inhibitors to achieve immunological nonresponsiveness. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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